REMARKS

Claims 1-41 are pending, and stand rejected in the present application. The Examiner has rejected Claims 1-41 on the following grounds:

1. The Claims have been objected to because of informalities with respect to numbering and a misspelled word.
2. The Abstract of the specification has been objected to because of its length.
3. The Oath/Declaration has been found to be defective in that it does not list the provisional application 60/159,689 for which priority is being requested.
4. The application has been found to be not in compliance with respect to Sequence Disclosures.
5. Claims 1-41 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.
6. Claims 1-14 and 26-36 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.
7. Claims 1-36 have been granted a priority date of 10/14/99, while claims 37-41 have been granted a priority date of 11/04/99.
8. Claims 1-7, 12-20 and 25-36 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Rader *et al.* (*Proc. Natl. Acad. Sci. USA* 95:8910-8915, 1998).
9. Claims 37-41 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Baca *et al.* (*Proc Natl Acad Sci USA* 94:10063-10068, 1997).
10. Claims 1-36 stand rejected under 35 U.S.C. § 103 (a), as allegedly obvious in light of Wu *et al.* (*Proc Natl Acad Sci USA* 95: 6037-6042, 1998) and further in view of Baca *et al.* (*J Biol Chem* 272:10678-10684, 1997) and Yelton *et al.* (*J Immunol* 155:1994-2004, 1995) and Studnicka *et al.* (*Protein Engineering* 7:805-814, 1994).

Applicants believe that the following remarks traverse the Examiner's objection to the Specification and rejection of the Claims. These remarks are presented in the same order as they appear above.

1. The Pending Claims Have Been Cancelled And New Claims Have Been Added

Without acquiescing to the Examiner's objections and rejections, but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have cancelled the pending claims and added new claims 42-51 to further define one embodiment of the invention. This renders moot the issues of claim numbering and typographical errors.

2. The Abstract is in Compliance

The Abstract has been amended to be in compliance with length requirements.

3. The Oath/Declaration Has Been Re-Submitted

The Oath/Declaration has been re-executed and re-submitted to list the provisional application 60/159,689 for which priority is being requested.

4. A Sequence Listing is Provided

The specification has been amended to provide sequence identifiers. Applicants' amendments do not introduce new matter.

The Examiner has requested that a Sequence Listing be provided. Applicants submit this Amendment and Response to provide as a separate part of the disclosure, a "Sequence Listing" pursuant to 37 C.F.R. §§ 1.821-1.825. Applicants submit herewith in paper copy and on floppy disk the Sequence Listing in computer readable form. The contents of the paper and computer readable copies are the same and include no new matter.

5. The Claims are Clear and Definite

The Examiner has rejected claims in the present application under 35 U.S.C. § 112, second paragraph, for multiple reasons. For clarity, Applicants will address each 35 U.S.C. § 112, second paragraph, rejection separately below, in sub-sections a-h.

a. The Examiner has found the abbreviations "CDRs", "CDR", CDR1", "CDR2" and "CDR3" to be indefinite. The Applicants have provided definitions for the abbreviations for complementarity-determining regions (see page 8 and Table 1 on page 9 of the specification as filed). Nonetheless, to further the prosecution, Applicants have spelled out the abbreviations

at their first appearance in each independent Claim and each dependent Claim in a new Claim set. Applicants respectfully request that the Amended Claims be considered allowable.

b. The Examiner has found Claims 1-41 indefinite for reciting "substantially the same" in Claims 1, 15 and 26. The Examiner finds the phrase to be unclear [Office Action mailed 3/15/01, p. 4]. Applicants respectfully direct the Examiner's attention to page 16 of the application as filed, where a definition for the term "substantially the same" when used in reference to binding affinity is provided:

> "....the term "substantially the same" when used in reference to binding affinity is intended to mean similar or identical binding affinities where one molecule has a binding affinity constant that is similar to another molecule within the experimental variability of the affinity measurement. The experimental variability of the binding affinity measurement is dependent upon the specific assay used and is known to those skilled in the art."

Thus, the Applicants do not agree with the Examiner and respectfully submit that one of skill in the art, when reading the Claims in light of definition provided will understand that "substantially the same" can encompass two molecules having an identical binding affinity, as well as two molecules having a similar binding affinity, in the context of the experimental measurement of binding affinity. In any event, it is believed that the structure of the new claims renders the question moot.

c. The Examiner has found Claims 1-41 to be indefinite for reciting "binding affinity substantially the same or greater than the donor CDR variable region" in Claims 1, 15 and 26. The Examiner finds the exact meaning of the phrase to be unclear for what the donor CDR variable region is being compared to, and whether binding to the same or different antigens is being compared.

The Applicants respectfully submit that the Claims are clear and definite as written, when considered in light of the teaching and definitions provided in the specification of the application as filed. As noted above (Section 5b of the instant response), the term "substantially the same" is defined on page 16 of the application as filed. Additionally, the applicants respectfully submit that the binding affinity of the altered variable regions is being compared to the binding affinity of the parent or donor variable region, in binding assays to the same antigen or target as recognized by the parent or donor variable region. This point is

made clearly in several sections of the instant specification (see, for example, pages 6, 7, 12 and 41). The teachings found at page 39, lines 21-27, and page 39, line 33-page 40, line 4, are particularly clear on this point:

> "Using any of the above described screening methods, as well as others known in the art, an altered variable region having binding affinity substantially the same or greater than the donor CDR variable region is identified by detecting the binding of at least one altered variable region within the population to its antigen or cognate ligand."
>
> "Comparison, either independently or simultaneously in the same screen, with the donor variable region will identify those binders that have substantially the same or greater binding affinity as the donor."

Furthermore, Example 1 describes screening variants for binding to the target antigen in comparison to the parent chimeric anti-CD40 Fab (see pages 52-53 of the specification as filed). Thus, Applicants do not agree with the Examiner and respectfully submit that the Claims are clear and definite as written, in light of the teachings of the specification, and request that the Examiner withdraw this rejection. In any event, it is believed that the structure of the new claims renders the question moot.

d. The Examiner finds Claim 2 indefinite for being unclear on the comparison of the binding of a variable region to that of a CDR. Applicants respectfully submit, that the claim as filed recites "...comparing the relative binding of said altered variable regions to said donor CDR **variable region**." (emphasis added). Thus, the claim as written, is directed to the comparison of two variable regions (*i.e.* the altered variable region and the donor CDR variable region). Applicants thus respectfully request that the Examiner withdraw this rejection, in light of this clarification. Alternatively, the Examiner may find that the current claims render the question moot.

e. The Examiner finds Claims 1-11, 13-24, 26-32 and 34-40 indefinite for reciting CDR amino acid positions as being unclear in the absence of the defining system for CDRs (*e.g.* Chothia, Kabat or some other system). The Examiner similarly finds Claims 6, 7, 11, 19, 20 and 24 to be indefinite for reciting framework regions, CDRs, or proximal to a CDR in the absence of a clear definition for how these regions are defined.

The Applicants respectfully submit that the specification as filed provides an adequate definition of which residues are considered CDR residues and which residues are not considered CDR residues (and are therefore framework residues). However, in consideration of the business interests of the Applicants, and solely to further the prosecution of the application, and expressly reserving the right to prosecute the same or similar claims in a future application, the Applicants have drafted new claims which recite that CDR amino acid positions are determined by the combined definitions of Kabat and Chothia, as presented in Table 1 of page 9 of the application as filed. Thus, when considering a given residue, Applicants respectfully submit that, should that particular residue fall into the definition of a CDR residue by either the Kabat or Chothia definition, then that residue is properly considered to be a CDR residue, and not a framework residue, for the purposes of the instant claims. In contrast, should a given residue not fall into the definition of a CDR residue by either of the Kabat or Chothia definitions presented in Table 1, page 9, then that residue is properly considered to be a framework residue.

f. Claim 13 stands rejected as reciting the limitation "said altered variable regions" in claim 5 with insufficient antecedent basis for this limitation in the claim 5. The new claims added in the instant amendment provide proper antecedent basis, and Applicants respectfully request that the Examiner withdraw this rejection.

g. Claims 9 and 22 are rejected as being indefinite for reciting "canonical framework" because the exact meaning of the phrase is not clear. The Examiner sates that it is not clear what defines the residue as "canonical" (page 5 of the Office Action mailed 3/15/01). Applicants respectfully refer the Examiner to page 21 (lines 8-17) of the specification as filed for a description of canonical framework residues:

> "Another criteria which can be used for determining the relevant amino acid positions to change, can be, for example, selection of framework residues that are known to be important, or contribute to CDR conformation. For example, canonical framework residues play such a role in CDR conformation or structure. Such residues can be considered to be relevant to change for a variety of reasons, including, for example, their new context of being associated with heterologous CDR sequences in the grafted variable region."

Additionally, on page 49 (lines 18-30) of the specification as filed:

"Based on structural and sequence analysis, antibody CDRs with the exception of HCDR3 display a limited number of main chain conformations termed canonical structures (Chothia and Lesk, (1987); Chothia et al., (1989)). Moreover, certain residues critical for determining the main chain conformation of the CDR loops have been identified (Chothia and Lesk, (1987); Chothia et al., (1989)). Canonical framework residues of murine anti-CD40 were identified therefore, and it was determined that amino acids at all critical canonical positions within the H and L chain frameworks of the human templates were identical to the corresponding murine residues."

Thus, canonical framework residues are described in the specification as those playing roles in CDR conformation or structure, and two scientific papers are cited for information regarding canonical framework residues and structures. Thus, the Applicants do not agree with the Examiner and respectfully submit that one of skill in the art would be able to use the teaching of the specification to determine canonical framework residues. In any event, it is believed that the structure of the new claims renders the question moot.

h. Claims 13-14 and 34-35 are rejected as being indefinite for reciting "wherein said altered variable regions are coexpressed with a light chain variable region" (claims 13 and 34) and "wherein said altered variable regions are coexpressed with a heavy chain variable regions" (claims 14 and 35). It is believed that Claims 44 and 49 make it clear that, in one embodiment, a two chain structure is expressed.

6. The Claims are Enabled

The Examiner has rejected Claims 1-14 and 26-36 under 35 U.S.C. 112, first paragraph as allegedly not being enabled for a method of optimizing the binding affinity of only a light chain or a heavy chain variable region of an antibody wherein any framework amino acid is substituted in the light or heavy chain (page 6 of the Office Action mailed 3/15/01). Similarly, on page 7 of the instant Office Action, the Examiner alleges that the specification does not enable a method for conferring donor binding or affinity maturation of a light chain or a heavy chain alone that binds antigen or wherein any framework region amino acids are substituted.

(i) The Applicants respectfully submit that the specification does provide a teaching for the ability of isolated chains to bind antigen (see page 41, lines 1-8). More to the point, Applicants note that the claims need not specify all the components or all of the steps of a method, since the term "comprise" or "comprising" permits the claim to cover (but not be limited to) other components and other steps.

(ii) With respect to framework residues and their alteration, the instant specification provides evidence that framework residues can be altered in such a way so as to obtain higher binding affinity. The Hu I combinatorial library of example 1 of the instant application comprises framework residues, and clones from this library were isolated which bound antigen with higher affinity. For example, clone 19C11 binds the CD40 receptor with higher affinity than the chimeric Fab (see page 54, lines 8-11 and Figure 2A).

With respect to Examiners rejection of original (and presently cancelled) Claims 1-14 and 26-36 for selection of any framework residue and antibody structure, the Examiner admits that the claims are enabled for selection of the one or more framework region amino acids by (i) differences in amino acid identity between donor and acceptor, (ii) solvent exposure and (iii) interaction with a CDR (page six of the Office Action mailed 3/15/01). Based on this admission of enablement, and without acquiescing to the Examiner's rejection, the applicants respectfully submit that the instant claims (i.e. claims 42-51) are fully enabled, as they further define one embodiment of the invention, namely that the acceptor framework positions that are changed are selected from among the acceptor framework positions that differ at the corresponding position compared to the donor framework.

7. Priority Dates

The Examiner has granted claims 1-36 a priority date of 10/14/99 and claims 37-41 a priority date of 11/04/99. Without agreeing with the Examiner, but to further the prosecution and pursue claims directed to one embodiment of the invention, Claims 37-41 have been cancelled (without prejudice to their prosecution in a future continuation application).

8. The Claims Are Not Anticipated

Claims 1-7, 12-20 and 25-36 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Rader *et al.* (*Proc. Natl. Acad. Sci. USA* 95:8910-8915, 1998). Claims 37-41 stand rejected under 35 U.S.C. § 102(b), as allegedly anticipated by Baca *et al.* (*Proc Natl Acad Sci USA* 94:10063-10068, 1997). Rader *et al.* does not anticipate the pending claims. Moreover, since Claims 37-41 have been cancelled, it is believed that the anticipation rejection based on Baca *et al.* is moot (although Applicants wish to stress that the claims have not been cancelled in response to the art rejection; Applicants do not agree with the rejection and reserve the right to prosecute Claims 37-41, or similar claims, in the future - at which point the missing features in the Baca *et al.* reference will be addressed).

The Examiner characterizes Rader *et al.* as teaching a method for affinity maturation of an antibody wherein the acceptor framework has many mutations and four of the CDRs are randomized. Applicants cannot agree with this characterization.

In the Rader reference, the antibody is humanized from the parent LM609. Rader *et al.* first isolate the cDNA encoding the parental LM609 antibody and use this to produce phage expressing LM609 Fab on their surface. See the Abstract: "The original sequences of the third CDRs of heavy and light chins, HCDR3 and LCDR3 were maintained and all other sequences were replaced by human sequences selected from phage-displayed antibody libraries." The first step of humanization is to produce Fabs with a library of light chains and a "fixed" chimeric heavy chain Fd (chimeric between original murine VH and human CH1). The light chain library preserves the murine LCDR3 (unaltered). Murine light chain FR4 has one residue which is altered to match the human sequence. Importantly, the remainder of the light chain (with grafted, unaltered murine LCDR3) library is essentially a pool of amplified human light chain sequences (amplified from healthy human bone marrow; i.e. FR1-CDR1-FR2-CDR2-FR3 are all human sequences selected from the bone marrow library). The Fabs (chimeric heavy chain Fd/ human light chain library pool with grafted LCDR3) were expressed and screened for antigen binding through several rounds of display.

The second step of humanization described by Rader *et al.* used the light chains from the selectants obtained in step 1 (above) to stabilize a library of heavy chains. The heavy chain library used human VH gene libraries (obtained by amplification of human bone

marrow; again FR1-CDR1-FR2-CDR2-FR3 are all from the human bone marrow library) "stitched" onto the Fd fragment above (note that the murine HCDR3 is present and unaltered).

Thus, the characterization by the Examiner does not appear to be correct. Neither the HCDR3 nor the LCDR3 is altered. The human CDRs selected from the bone marrow library are derived from human sequences. Finally, acceptor framework residues are not changed.

Turning now to the claims, step (b) of Claim 1 specifies synthesizing ii) a second population of oligonucleotides, comprising oligonucleotides encoding modified portions of a heavy chain variable region framework, said modified portion *containing a plurality of changed amino acids at one or more positions when compared to said acceptor framework region reference sequence*, wherein said framework positions that are changed are selected from among said acceptor framework positions of said second reference sequence that differ at the corresponding position compared to the donor framework positions of said first reference sequence. Thus, the fact that the Rader reference does not teach that acceptor framework residues are changed - alone[2] - makes the reference an improper 102 reference.

9. The Claims Are Not Obvious

Claims 1-36 stand rejected under 35 U.S.C. § 103 (a), as allegedly obvious in light of Wu *et al.* (*Proc Natl Acad Sci USA* 95: 6037-6042, 1998) and further in view of Baca *et al.* (*J Biol Chem* 272:10678-10684, 1997) and Yelton *et al.* (*J Immunol* 155:1994-2004, 1995) and Studnicka *et al.* (*Protein Engineering* 7:805-814, 1994). Applicants disagree.

First, the Examiner's 103 rejection is fundamentally flawed by lack of any basis for combining the references. Each of the references teaches a different approach. There is no basis for believing that one skilled in the art would combine teachings when the references themselves are not consistent in their approach. The Examiner must provide a basis for combining art prior to considering the combination. Indeed, the requirement that the Examiner make a showing of a suggestion, teaching or motivation to combine the prior art references is "an essential evidentiary component of an obviousness holding." *C.R. Bard, Inc. v. M3 Sys. Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998). There are three sources for this

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[2] There are many other differences (*e.g.* synthesis of the oligonucleotides specified, creation of overlapping oligonucleotides, etc.). However, one difference is sufficient to avoid a 102 rejection.

evidentiary component: the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996). The suggestion most often comes from the teachings of the pertinent references. *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998). Nonetheless, regardless of the source of the requisite evidence, the Examiner's showing "must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 1000 (Fed. Cir. 1999).

Importantly, since an Examiner is NOT one skilled in the art (under the law), the Examiner's opinion on what one skilled in the art might believe does not count. *In re Rijckaert*, 9 F.3d 1531, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) ("[T]he examiner's assumptions do not constitute the disclosure of the prior art."). Of course, if the Examiner has knowledge of relevant facts which are used to make the rejection, the Examiner is free to used those facts - but only if submitted in the form of an affidavit. *See* 37 CFR 1.107(b). In the present case, the Examiner has submitted no such affidavit.

Indeed, the Examiner has provided only the Examiner's opinion and conclusory statements - this is not the requisite "evidence" needed to support the combination. The Examiner simply asserts - without a basis - that "it would be obvious" for one skilled in the art to combine the teachings. The above-cited case law shows that this is not adequate and the Examiner has not satisfied the requirements for combining the art.

Second, even if the art is combined (improperly), elements of the claims are not taught. By way of example only, many of the cited references work with a template (*e.g.* a murine template) and make point mutations. The present claims (which represent but one embodiment of the present invention) utilize reference sequences to synthesize oligos which (when combined as specified) generate populations of nucleic acids encoding both i) framework changes and ii) changes in one or more CDRs. This allows for the more efficient screening of candidates to identify higher binding antibodies in binding assays. Even if the cited art is combined in the manner proposed by the Examiner, these features of the present claims are not taught. Therefore, the 103 rejection must be withdrawn.

CONCLUSION

Applicants believe that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617)-252-3353.

Dated: August 15, 2001

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APPENDIX I
MARKED-UP VERSION OF REWRITTEN SPECIFICATION
PURSUANT TO 37 CFR § 1.121 (c)(1)(ii)

On page 4, please delete the paragraph beginning on line 29 and ending on line 30, and replace with the following paragraph:

Figure 1 (SEQ ID NOS: 1 - 4) shows the alignment of anti-CD40 variable region and human template amino acid sequences.

IN THE ABSTRACT

Please delete the paragraph beginning on page 74, line 2 and ending on page 75, line 25 and replace with the following paragraph:

The invention provides a method of conferring donor CDR binding affinity onto an antibody acceptor variable region framework. [The method consists of: (a) constructing a population of altered antibody variable region encoding nucleic acids, said population comprising encoding nucleic acids for an acceptor variable region framework containing a plurality of different amino acids at one or more acceptor framework region amino acid positions and donor CDRs containing a plurality of different amino acids at one or more donor CDR amino acid positions; (b) expressing said population of altered variable region encoding nucleic acids, and (c) identifying one or more altered variable regions having binding affinity substantially the same or greater than the donor CDR variable region. The acceptor variable region framework can be a heavy or light chain variable region framework and the populations of heavy and light chain altered variable regions can be expressed alone to identify heavy or light chains having binding affinity substantially the same or greater than the donor CDR variable region. The populations of heavy and light chains additionally can be coexpressed to identify heteromeric altered variable region binding fragments.] The invention also provides a method of simultaneously grafting and optimizing the binding affinity of a variable region binding fragment. [The method consists of: (a) constructing a population of altered heavy chain variable region encoding nucleic acids comprising an acceptor variable region framework containing donor CDRs and a plurality of different amino acids at one or more framework region and CDR amino acid positions; (b) constructing a

population of altered light chain variable region encoding nucleic acids comprising an acceptor variable region framework containing donor CDRs and a plurality of different amino acids at one or more framework regions and CDR amino acid positions; (c) coexpressing said populations of heavy and light chain variable region encoding nucleic acids to produce diverse combinations of heteromeric variable region binding fragments, and (d) identifying one or more heteromeric variable region binding fragments having affinity substantially the same or greater than the donor CDR heteromeric variable region binding fragment.] A method of optimizing the binding affinity of an antibody variable region is also provided. [The method consists of: (a) constructing a population of antibody variable region encoding nucleic acids, said population comprising two or more CDRs containing a plurality of different amino acids at one or more CDR amino acid positions; (b) expressing said population of variable region encoding nucleic acids, and (c) identifying one or more variable regions having binding affinity substantially the same or greater than the donor CDR variable region. The variable region populations can be heavy or light chains and can be expressed as individual populations or they can be coexpressed to produce heteromeric variable region binding fragments.]